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Letter to the Editor

## Ultra-Treatment Resistant Schizophrenia- Where Do We Stand?

The term ultra-treatment resistant schizophrenia (UTRS) is used to designate cases showing inadequate response (or lack thereof) to adequate trial of clozapine (CLOZ) after excluding confounders (Khouadja et al., 2017) that might otherwise compromise response (e.g. substance abuse, treatment non-adherence) Due to negative connotations and therapeutic nihilism the term might imply, some have proposed clozapine-resistant schizophrenia (CRS) instead. This is more apt technically confirming an adequate trial of CLOZ has been undertaken and response has proven suboptimal. This is advantageous excluding those eligible for CLOZ trial that have been denied it, though.

CLOZ remains the only antipsychotic that is FDA-approved for treatment resistant schizophrenia (TRS) besides antisuicidality (Kishi et al., 2013). A recent meta-analysis has reported a response rate of circa 40% (Siskind et al., 2018).

Although, there remains no operationalized definition of UTRS, some have proposed these criteria (Mouaffak et al., 2006); adequate dose of CLOZ with plasma level > 350 ng/mL, adequate duration for 8 weeks, with no significant improvement defined as < 20% decrease on BPRS, current severity defined as BPRS ≥ 45, CGI-S ≥ 4 and ≥ 4 on 2/4 positive items on BPRS, and poor functioning over 5 years. Some limitations in these criteria are noteworthy mentioning here.

Current evidence, however, suggests early and effective treatment in schizophrenia is associated with improved outcome. This would strongly argue against a 5-year delay in access to CLOZ. Moreover, it has been demonstrated that delayed CLOZ use in those with treatment-resistant schizophrenia compromises response suggesting one can also evolve into CRS (Yoshimura et al., 2017).

Another drawback is refractory positive symptom domain remain central to defining UTRS. This belittles how other symptom domains (esp. negative/cognitive) impact functionality. In the same vein, it has been noted that, whilst CLOZ can tackle positive symptom domain, this does not necessarily translate into parallel improvement in functionality (Lee et al., 2014).

Sorely, no clinical variables, nor pharmacogenetics, have been identified that are unequivocally associated with clinical response to CLOZ (Bruijnzeel et al., 2014).

Considerable work has focused on the role of glutamate in TRS (Howes et al., 2015). This has extended to CRS as well.

A number of different strategies have been deployed. These include adding a second antipsychotic to CLOZ (data in favour of aripiprazole, amisulpiride, ziprasidone), antidepressants, mood stabilizers, glutamate modulators, etc …

Some augmentations may be useful to manage clozapine adverse effects such as metabolic syndrome (e.g. aripiprazole add-on), seizures (valproate), sialorrhea (amitryptiline), neutropenia (lithium), to address pharmacokinetics and 'pseudo-resistance' (e.g. cautiously monitored fluvoxamine add-on) or to tackle specific comorbidities (e.g. depression or OCD with sertraline). Others might help with target symptom domains (e.g. memantine for cognitive, mirtazapine for negative, lamotrigine for positive domains)

Whilst there is trial evidence to support a number of these aforementioned strategies, robust meta-analytic data are generally lacking. A robust effect with ECT has been noted in a meta-analysis but this was only confined to one RCT and three open trials (Lally et al., 2016).

Some 'outside the box' agents include pimavanserin, 5HT2A inverse agonist (FDA approved for Parkinson's disease psychosis) has been shown to be promising in a case series of CRS; minocycline, a tetracycline antibiotic with putative anti-inflammatory and neuro-protective properties; allopurinol, an anti-gout agent, a xanthine oxidase inhibitor enhancing adenosinergic activity; the herbal ginkgo biloba, …

Where favourable findings have been reported, the magnitude of change is frequently modest and of questionable clinical significance. Even reports of clinical worsening have been reported.

Given the neuroprogressive devastating nature and heterogeneity of UTRS, hence, it is very unlikely that one strategy will be effective for all patients. This should better be used on a case-by-case basis.

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Ahmed Naguy*
*Kuwait Centre for Mental Health Jamal Abdul-Nassir St., 21315, shuwaikh, Kuwait*
*E-mail address:* ahmednagy@hotmail.co.uk.

Bibi Alamiri
*Tufts University, Medford, US*

* Corresponding author.